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09/756,899	01/09/2001	Franciscus Antonius, M. Redegeld	4692US	1305

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13

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/756,899	Applicant(s) REDEGELD ET AL.
	Examiner " Neon" Phuong Huynh	Art Unit 1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 January 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,10-13,16-25,31 and 32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,10-13,16-25,31 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 January 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-5, 10-13, 16-25 and 31-32 are pending.

2. In view of the amendment filed 1/2/03, the following rejections remain.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-5, 10-13, 16-25 and 31-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a composition comprising a peptide consisting of SEQ ID NO: 1 that inhibits the binding of free light chain of immunoglobulin (LC) to mast cells *in vitro* wherein when said peptide is in the presence of an equimolar quantity of the free light chain of immunoglobulin in a solution, the free light chain of immunoglobulin's binding to said mast cells is reduced by at least 5% for inhibiting the binding of free light chain of immunoglobulin, (2) the said composition wherein the peptide also binds to the free light chain of immunoglobulin; competes with a peptide for binding to the free light chain of immunoglobulin *in vitro*, wherein said peptide has the amino acid sequence consisting of AHWSGHCCL (SEQ ID NO: 1) and wherein when said peptide is present in equimolar amounts in a solution, said peptide reduces binding of said peptide to said free light chain of immunoglobulin by at least 5% or 10%, (3) the said composition wherein the peptide reduces the binding of said peptide to the free light chain of immunoglobulin by at least 25%, 50%, 75% or 90% *in vitro*, (4) the said composition wherein the peptide has a mass of less than 10 kDal, or 2 kDal and inhibits the binding of free light chain of immunoglobulin (LC) to mast cells *in vitro,* (5) a composition wherein the peptide consisting of SEQ ID NO: 1 produced by the process recited in claim 22 wherein said peptide has a mass less than 10 kDal or a mass less than 2 kDal, and the said peptide is an LC-binding peptide fragment of Tamm-Horsfall glycoprotein for inhibiting the binding of free light chain of immunoglobulin (LC) to mast cells *in vitro* or brochoconstriction in vivo, **does not** reasonably provide enablement for (1) *any* pharmaceutical composition comprising *any* "peptide" that inhibits binding of free light chain of immunoglobulin (LC) to mast cells: wherein when the peptide is in the presence of an equimolar quantity of the free light chain of immunoglobulin in a

solution, the free light chain of immunoglobulin's bindings to said mast cells is reduced by at least 5%, (2) the pharmaceutical composition mentioned above wherein the peptide also binds to the free light chain of immunoglobulin; competes with any peptide for binding to the free light chain of immunoglobulin, wherein said peptide has the amino acid sequence AHWSGHCCL (SEQ ID NO: 1) and wherein when said peptide and said second peptide are present in equimolar amounts in a solution, said peptide reduces binding of said second peptide to said free light chain of immunoglobulin by at least 5% or by at least 10%, (3) the pharmaceutical composition mentioned above wherein the peptide also binds to the free light chain of immunoglobulin; competes with a peptide for binding to the free light chain of immunoglobulin, wherein the peptide is *any* peptidomimeticum, (4) the pharmaceutical composition mentioned above wherein the peptide also binds to the free light chain of immunoglobulin; competes with a peptide for binding to the free light chain of immunoglobulin, wherein said peptide is *any* "pharmaceutical acceptable compound", (5) *any* pharmaceutical composition for treating any disease state in a subject, said disease state characterized by exhibiting: (i) a serum concentration of free light chain of immunoglobulin in serum of at least 8 mg/ml; (ii) a spinal fluid concentration of free light kappa-chain of immunoglobulin of at least 70 µg/l and/or (iii) a spinal fluid concentration of free lamda-chain of immunoglobulin of at least 300 µg/l; said pharmaceutical composition comprising any peptide, wherein when the peptide is in the presence of an equimolar quantity of free light chain of immunoglobulin (LC), the peptide reduces the equimolar quantity of LC's binding to mast cells present in solution therewith by at least 5%, (6) *any* pharmaceutical composition mentioned above wherein the peptide inhibits LC's binding to mast cells present in solution by at least 10%, (7) *any* pharmaceutical composition mentioned above wherein the disease is selected from the group consisting of asthma, allergy, chronic inflammatory bowel disorders, viral injection and multiple sclerosis, (8) *any* pharmaceutical composition comprising *any* peptide that, in the presence of an equimolar quantity of free light chain of immunoglobulin (LC), reduces the equimolar quantity of LC's binding to mast cells present in the solution by at least 5%, and a pharmaceutically acceptable carrier or diluent, (9) *any* pharmaceutical composition mentioned above wherein the peptide also binds to the free light chain of immunoglobulin; competes with a peptide for binding to the free light chain of immunoglobulin, wherein said peptide has the amino acid sequence AHWSGHCCL (SEQ ID NO: 1) reduces the binding of said second peptide to the free light chain of immunoglobulin by at least 25%, 50%, 75%, or at least 90%, (10) *any* pharmaceutical composition wherein the peptide is any peptidomimeticum that has a mass of less

than 10 kDal, (11) *any* pharmaceutical composition wherein the peptide is any pharmaceutical acceptable compound that has a mass of less than 2 kDal, (12) any pharmaceutical composition comprising any peptide produced by a process as set forth in claim 22, (13) any pharmaceutical composition wherein the peptide is any pharmaceutical acceptable compound that has a mass of less than 2 kDal, (14) any pharmaceutical composition comprising any peptide produced by a process as set forth in claim 22 characterized in that the peptide has a mass less than 10 kDal or 2 kDal, (15) *any* pharmaceutical composition comprising any peptide produced by a process as set forth in claim 22 wherein the peptide is any LC-binding peptide fragment of Tamm-Horsfall glycoprotein or any derivative thereof, (16) *any* pharmaceutical composition comprising any peptide that, in the presence of an equimolar quantity of free light chain of immunoglobulin (LC), reduces the equimolar quantity of LC's binding to mast cells present in the solution by at least 5% and a pharmaceutically acceptable carrier or diluent wherein the peptide binds LC; competes for binding with LC and any second peptide with the amino acid sequence AHWSGHCCL (SEQ ID NO: 1) and reduces binding of said second peptide with LC by at least 5% when the peptide and the second peptide are present in a solution with said LC in equimolar amounts, and (17) *any* pharmaceutical composition comprising *any* peptide that, in the presence of an equimolar quantity of free light chain of immunoglobulin (LC), reduces the equimolar quantity of LC's binding to mast cells present in the solution by at least 5% and a pharmaceutically acceptable carrier or diluent wherein the peptide has a mass of less than 10 kDal for treating any disease such as chronic inflammatory bowel disorders, viral infection, and multiple sclerosis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only three peptides selected from the group consisting of SEQ ID NO: 1-3 and only peptide consisting of SEQ ID NO: 1 at 0.25mg/ml and 0.5 mg/ml can inhibit

the free light chain of Ig binding to mast cells (See page 8, and Fig 1 of the specification). The specification also discloses that TNP specific Ig light chain but not the Ig heavy chain. The specification also discloses that mast cell are important in sensitization of mice to antigen such as PSA (See page 9-10 Table 1, 2 and 3 of the specification). The specification further discloses that immunoglobulin light chain also binds to human uromodulin, which is a Tamm-Horsefall glycoprotein (THP) (See page 11 of the specification).

The specification does not teach how to make and use *any* pharmaceutical composition comprising *any* "peptide" because there is insufficient guidance as to the structure such as amino acid sequence of any undisclosed "peptide", let alone having a specific function that could be used for a pharmaceutical composition for treating any disease. Further, there is insufficient in vivo working example in the specification demonstrating that any undisclosed peptide, second peptide "has" SEQ ID NO: 1, *any* fragment of Tamm-Horsfall glycoprotein and *any* derivative thereof could prevent the interaction of Ig light chain from binding to mast cells, in turn, would be useful for treating any disease such as chronic inflammatory bowel disorders, viral infection and multiple sclerosis.

With regard to second peptide "has" the amino acid of SEQ ID NO: 1, the term "has" is open-ended. It expands the second peptide to include additional amino acid residues at either or both ends of the second peptide. There is insufficient guidance as to the what type and number of amino acids within the peptide of SEQ ID NO: 1 can be added and whether the peptide having extra amino acids would retain the structure and function as SEQ ID NO: 1. Given the indefinite number of undisclosed second, it is unpredictable which undisclosed second peptide could compete with the undisclosed peptide for binding to the free light chain, in turn, would be useful for treating any disease.

With regard to peptide "is" an LC-binding peptide fragment of Tamm-Horsfall glycoprotein or any "derivative thereof", there is insufficient guidance as to the amino acid sequence of the fragment of Tamm-Horsfall glycoprotein that binds LC. Further the term "is" is open-ended. It expands the undisclosed fragment of Tamm-Horsfall glycoprotein to include additional amino acids at either of both ends. There is insufficient guidance as to the amino acids can be added and whether after addition of amino acids would retain the structure and function of Tamm-Horsfall glycoprotein that binds LC. The term "derivative" without amino acid sequence or SEQ ID NO has no structure, much less function. Further, there is insufficient in vivo working example that any peptide and derivative thereof is effective for treating any disease.

With regard to "Tamm-Horsfall glycoprotein derivative thereof", there is no guidance as to which amino acids within the full-length amino acid sequence of Tamm-Horsfall glycoprotein can be deleted or added and after modification would retain the structure and function of Tamm-Horsfall glycoprotein. Given the indefinite number of undisclosed LC-binding peptide fragment and derivative thereof, it is unpredictable which undisclosed Tamm-Horsfall glycoprotein peptide fragment and derivative thereof would bind to LC, in turn, useful as a pharmaceutical composition for treating any disease.

Ngo *et al*, of record, teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). Given the lack of guidance and working examples, predicting what changes can be made to the undisclosed peptide that after substitution, deletion, insertion and/or modification will retain both structure and have similar function as peptide of SEQ ID NO: 1 is unpredictable.

Further, there are insufficient in vivo working examples that *any* peptide mentioned above could treat just any disease such as chronic inflammatory bowel disorders, viral infection and multiple sclerosis.

Redegeld *et al*, of record, teach that currently no pathophysiological role for secreted IgLCs has been documented. Free light chain immunoglobulin does not activate gamma chain of the Fcγ chain associated with the Fc receptors such as FcεRI, and FcγRIII, which are expressed on mast cell. IgLC mediated mast cells is independent of complement activation. Redegeld *et al* further teach IgLC antagonist such as F991, which is a 9mers peptide (AHWSGHCCL) can prevent hapten-induced ear swelling, which is contact delayed hypersensitivity reaction. Given that currently no pathophysiological role for secreted IgLCs has been documented, it is not predictable which undisclosed peptide would be effective in treating any disease such as viral infection and multiple sclerosis. Without knowing the specific structure of undisclosed "peptide", "peptide fragment" of Tamm-Horsefall glycoprotein, "Tamm-Horsefall glycoprotein derivative thereof" and not to mentioned peptidomimeticum and *any* undisclosed compound, it is unpredictable which undisclosed peptide, Tamm-Horsefall glycoprotein fragment and derivative thereof would be useful for inhibiting the binding of free light chain immunoglobulin to mast cells, in turn, for treating just *any* disease. Even if the pharmaceutical composition is limited to a peptide consisting of SEQ ID NO: 1, there is insufficient in vivo working example that the

peptide of SEQ ID NO: 1 could treat inflammatory bowel disease, viral infection, much less multiple sclerosis. Further, given that the claimed compound has to be in equimolar amounts in a solution in order to reduce the binding of the free light chains to mast cells even in vitro only by 5% when in vivo mast cells are usually reside in tissues and very heterogeneous in nature, it is not obvious how any peptide when in equimolar concentration as the free light chains of the immunoglobulin in serum at least 8 mg/l, or in spinal fluid concentration of at least 70 μg/l and or in spinal fluid at least 300 μg/l would be effective for treating any disease in a subject such as viral infection and multiple sclerosis since free light chain immunoglobulin does not even activate gamma chain of the Fcγ chain associated with the Fc receptors such as FcεRI, and FcγRIII that are expressed on mast cell as taught by Redegeld *et al* discussed supra.

With regard to multiple sclerosis, not only there is a lack of guidance as to the structure of the undisclosed peptide, there is insufficient in vivo working examples demonstrating that any undisclosed peptide could treat multiple sclerosis. The specification discloses only measuring bronchoconstriction in mast cell deficient mice after sensitization of mice to TNP-specific Ig LC. The specification does not adequately teach how to effectively treat any disease such as multiple sclerosis, viral infection and inflammatory bowel disease in humans by administering any undisclosed peptide. The specification does not teach how to extrapolate data obtained from measuring bronchoconstriction in mast cell deficient mice after sensitization of mice to TNP-specific Ig LC to treat any disease such as multiple sclerosis, inflammatory bowel disease and viral infection, commensurate in scope with the claimed invention.

Van Noort *et al*, of record, teach that models of autoimmune diseases depends on numerous factors such as animal strains used, the antigens used, the immunization protocol used, especially some protocol for EAE that result in a single acute episode while others induce chronic relapsing disease (See page 168-169, in particular). Van Noort *et al* teach that induction of EAE with MBP does not result in the development of relapse and the clinical course may be different than that after treatment with other antigen such as SCH and PLP (See page 170, in particular). Given the teachings of Van Noort et al, it is not clear to one skilled in the art that measuring bronchoconstriction in mast cell deficient mice as taught in the specification is an appropriate model for multiple sclerosis, let alone viral infection. Further, given the indefinite number of undisclosed peptide, and that autoimmune diseases differ with respect to animal strains used, the antigens used, the immunization protocol used in light of the teaching of the specification with respect to inhibiting the binding of immunoglobulin light chain to mast cell in the literature, it

would take undue amount of experimentation to practice the claimed invention. Given the undisclosed peptide in the pharmaceutical composition is not enabled, it follows that any peptide that reduces the binding of *any* peptide to the free light chain of immunoglobulin by at least 25%, 50% 75% or 90% is not enabled. It also follows that any undisclosed peptides in the pharmaceutical composition that has a mass of less than 10 kDal or 2 kDal is not enabled.

With regard to claim 22, there is insufficient guidance and lack of working examples for screening compound or any compound produced by a process recited in claim 22 where the screening process comprising incubating *any* peptide with an admixture comprising LC and *any* labeled peptide, said labeled peptide comprising any peptide and label and said peptide is capable of binding the free light chain of immunoglobulin and competing with a peptide (SEQ ID NO: 1) for binding to the free light chain and isolating the compounds which bind LC and complete with the peptide. Further, the peptide is *any* LC-binding peptide fragment of Tamm-Horsfall glycoprotein or *any* "derivative thereof", there is insufficient guidance and working example as to which undisclosed peptide fragment or derivative of Tamm-Horsfall glycoprotein is capable of binding to LC. Since the LC-binding peptide fragment and derivative thereof are not enabled, it follows that any pharmaceutical composition comprising any peptide produced by as set forth in claim 22 is not enabled.

For these reasons, it would require undue experimentation even for one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992). In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 1/2/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) the claims have been amended to a "pharmaceutical composition" comprising a "peptide" instead of being directed to any compound. (2) Examples 2-4 are working examples of in vivo experiments performed on sensitized mice and indicating that the claimed peptide can be applied in different ways.

In response to applicant's argument that the claims have been amended, the amended claims still recite any "peptide". The specification does not teach how to make and use *any* pharmaceutical composition comprising *any* "peptide" because there is insufficient guidance as to the structure such as amino acid sequence of any undisclosed "peptide", let alone having a specific function that could be used for a pharmaceutical composition for treating any disease. It is unpredictable which undisclosed second peptide could compete with the undisclosed peptide for binding to the free light chain, in turn, would be useful for treating any disease such as chronic inflammatory bowel disorders, viral infection and multiple sclerosis. Further, the specification does not adequately teach how to effectively treat any disease such as multiple sclerosis, viral infection and inflammatory bowel disease in humans by administering any undisclosed peptide using the inappropriate model such as measuring bronchoconstriction in mast cell deficient mice. The specification does not teach how to extrapolate data obtained from measuring bronchoconstriction in mast cell deficient mice after sensitization of mice to TNP-specific Ig LC to treat any disease such as multiple sclerosis and viral infection, commensurate in scope with the claimed invention.

5. Claims 1-5, 10-13, 16-25 and 31-32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) *any* pharmaceutical composition comprising *any* "peptide" that inhibits binding of free light chain of immunoglobulin (LC) to mast cells: wherein when the peptide is in the presence of an equimolar quantity of the free light chain of immunoglobulin in a solution, the free light chain of immunoglobulin's bindings to said mast cells is reduced by at least 5%, (2) the pharmaceutical composition mentioned above wherein the peptide also binds to the free light chain of immunoglobulin; competes with any peptide for binding to the free light chain of immunoglobulin, wherein said peptide has the amino acid sequence AHWSGHCCL (SEQ ID NO: 1) and wherein when said peptide and said second peptide are present in equimolar amounts in a solution, said peptide reduces binding of said second peptide to said free light chain of immunoglobulin by at least 5% or by at least 10%, (3) the pharmaceutical composition mentioned above wherein the peptide also binds to the free light chain of immunoglobulin; competes with a

peptide for binding to the free light chain of immunoglobulin, wherein the peptide is *any* peptidomimeticum, (4) the pharmaceutical composition mentioned above wherein the peptide also binds to the free light chain of immunoglobulin; competes with a peptide for binding to the free light chain of immunoglobulin, wherein said peptide is *any* "pharmaceutical acceptable compound", (5) *any* pharmaceutical composition for treating any disease state in a subject, said disease state characterized by exhibiting: (i) a serum concentration of free light chain of immunoglobulin in serum of at least 8 mg/ml; (ii) a spinal fluid concentration of free light kappa-chain of immunoglobulin of at least 70 μg/l and/or (iii) a spinal fluid concentration of free lamda-chain of immunoglobulin of at least 300 μg/l; said pharmaceutical composition comprising any peptide, wherein when the peptide is in the presence of an equimolar quantity of free light chain of immunoglobulin (LC), the peptide reduces the equimolar quantity of LC's binding to mast cells present in solution therewith by at least 5%, (6) *any* pharmaceutical composition mentioned above wherein the peptide inhibits LC's binding to mast cells present in solution by at least 10%, (7) *any* pharmaceutical composition mentioned above wherein the disease is selected from the group consisting of asthma, allergy, chronic inflammatory bowel disorders, viral injection and multiple sclerosis, (8) *any* pharmaceutical composition comprising *any* peptide that, in the presence of an equimolar quantity of free light chain of immunoglobulin (LC), reduces the equimolar quantity of LC's binding to mast cells present in the solution by at least 5%, and a pharmaceutically acceptable carrier or diluent, (9) *any* pharmaceutical composition mentioned above wherein the peptide also binds to the free light chain of immunoglobulin; competes with a peptide for binding to the free light chain of immunoglobulin, wherein said peptide has the amino acid sequence AHWSGHCCL (SEQ ID NO: 1) reduces the binding of said second peptide to the free light chain of immunoglobulin by at least 25%, 50%, 75%, or at least 90%, (10) *any* pharmaceutical composition wherein the peptide is any peptidomimeticum that has a mass of less than 10 kDal, (11) *any* pharmaceutical composition wherein the peptide is any pharmaceutical acceptable compound that has a mass of less than 2 kDal, (12) any pharmaceutical composition comprising any peptide produced by a process as set forth in claim 22, (13) any pharmaceutical composition wherein the peptide is any pharmaceutical acceptable compound that has a mass of less than 2 kDal, (14) any pharmaceutical composition comprising any peptide produced by a process as set forth in claim 22 characterized in that the peptide has a mass less than 10 kDal or 2 kDal, (15) *any* pharmaceutical composition comprising any peptide produced by a process as set forth in claim 22 wherein the peptide is any LC-binding peptide fragment of Tamm-Horsfall

glycoprotein or any derivative thereof, (16) *any* pharmaceutical composition comprising any peptide that, in the presence of an equimolar quantity of free light chain of immunoglobulin (LC), reduces the equimolar quantity of LC's binding to mast cells present in the solution by at least 5% and a pharmaceutically acceptable carrier or diluent wherein the peptide binds LC; competes for binding with LC and any second peptide with the amino acid sequence AHWSGHCCL (SEQ ID NO: 1) and reduces binding of said second peptide with LC by at least 5% when the peptide and the second peptide are present in a solution with said LC in equimolar amounts, and (17) *any* pharmaceutical composition comprising *any* peptide that, in the presence of an equimolar quantity of free light chain of immunoglobulin (LC), reduces the equimolar quantity of LC's binding to mast cells present in the solution by at least 5% and a pharmaceutically acceptable carrier or diluent wherein the peptide has a mass of less than 10 kDal for treating any disease such as chronic inflammatory bowel disorders, viral infection, and multiple sclerosis.

The specification discloses only three peptides selected from the group consisting of SEQ ID NO: 1-3 and only peptide of SEQ ID NO: 1 at 0.25mg/ml and 0.5 mg/ml can inhibit free light chain of Ig binding to mast cells (See page 8, and Fig 1 of the specification). The specification also discloses that TNP specific Ig light chain but not the Ig heavy chain and mast cell are important in sensitization of mice to antigen such as PSA (See page 9-10 Table 1, 2 and 3 of the specification). The specification further discloses that immunoglobulin light chains also binds to human uromodulin, which is a Tamm-Horsefall glycoprotein (THP) (See page 11 of the specification).

With the exception of the specific peptides mentioned above, there is insufficient written description about the structure associated with function of *any* peptide that inhibits binding of free light chain of immunoglobulin (LC) to mast cells because a peptide in the absence of amino acid sequence or SEQ ID NO has no structure, much less function.

Further, there is insufficient written description about the structure associated with function of *any* second peptide "has" the amino acid sequence of SEQ ID NO: 1 for treating any disease because the term "has" is open-ended. It expands the second peptide to include additional amino acid residues at either or both ends of the second peptide. There is adequate written description about the undisclosed amino acids to be added to the second peptide, let alone for a pharmaceutical composition for treating any disease such as chronic inflammatory bowel disorders, viral infection, and multiple sclerosis.

With regard to *any* peptide is any fragment of LC-binding peptide of Tamam-Horsfall glycoprotein or *any* derivative thereof, there is inadequate written description about the LC-binding peptide of Tamam-Horsfall because any fragment or derivative without amino acid sequence or SEQ ID NO: has no structure. Further, the specification discloses only peptide having the amino acid sequence consisting of SEQ ID NO: 1-3. Given the indefinite number of undisclosed derivative, there is inadequate written description about the structure, much less about the function of any undisclosed Tamam-Horsfall derivative thereof for treating any disease.

With regard to pharmaceutical composition comprising any undisclosed peptide for treating any disease such as chronic inflammatory bowel disease, viral infection, and multiple sclerosis, the specification discloses only **one** working peptide consisting of SEQ ID NO: 1 that inhibits the binding of free light chain of immunoglobulin to mast cells *in vitro* and inhibition of bronchial constriction in vivo. Given the lack of any additional peptide for treating any disease such as chronic inflammatory bowel disorders, viral infection, and multiple sclerosis, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of peptides to describe the genus. It also follows that the pharmaceutical composition for treating any disease such as inflammatory bowel disease, viral infection, and multiple sclerosis is not adequately described. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 1/2/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) the claims have been amended to a "pharmaceutical composition" comprising a "peptide" instead of being directed to any compound. (2) With regard to claim 22, the claim is directed to a pharmaceutical composition including a peptide produced by a process. The process includes screening a series of peptides for each of the peptide's capacity to bind to an immunoglobulin's free light chain and compete with a peptide of SEQ ID NO: 1. Since the process has been described for detecting peptides that bind other proteins, IgLC binding peptides can be selected using the process of claim 22 without undue experimentation.

In response to applicant's argument that the claims have been amended, the amended claims still recite any "peptide". With the exception of the specific peptides mentioned above,

there is insufficient written description about the structure associated with function of *any* peptide that inhibits binding of free light chain of immunoglobulin (LC) to mast cells because a peptide in the absence of amino acid sequence or SEQ ID NO has no structure, much less function. Further, there is insufficient written description about the structure associated with function of *any* second peptide "has" the amino acid sequence of SEQ ID NO: 1 for treating any disease because the term "has" is open-ended. It expands the second peptide to include additional amino acid residues at either or both ends of the second peptide. There is adequate written description about the undisclosed amino acids to be added to the second peptide, let alone for a pharmaceutical composition for treating any disease.

In response to Applicant's argument that claim 22 is directed to a pharmaceutical composition including a peptide produced by a process, the specification discloses only three peptides selected from the group consisting of SEQ ID NO: 1-3 and only peptide of SEQ ID NO: 1 at 0.25mg/ml and 0.5 mg/ml can inhibit free light chain of Ig binding to mast cells (See page 8, and Fig 1 of the specification). The specification also discloses that TNP specific Ig light chain but not the Ig heavy chain and mast cell are important in sensitization of mice to antigen such as PSA (See page 9-10 Table 1, 2 and 3 of the specification). The specification further discloses that immunoglobulin light chains also bind to human uromodulin, which is a Tamm-Horsefall glycoprotein (THP) (See page 11 of the specification). There is inadequate written description about pharmaceutical composition for treating disease such as chronic inflammatory bowel disorders, viral infection, and multiple sclerosis.

There is inadequate written description about structure of any peptide produced by the process of claim 22, much less the structure of any peptide is any fragment of LC-binding peptide of Tamam-Horsfall glycoprotein or *any* derivative thereof because any fragment or derivative without amino acid or SEQ ID NO: has no structure. Further, the specification discloses only peptide having the amino acid sequence consisting of SEQ ID NO: 1-3. With regard to pharmaceutical composition comprising any undisclosed peptide for treating any disease such as chronic inflammatory bowel disease, viral infection, and multiple sclerosis, the specification discloses only **one** working peptide consisting of SEQ ID NO: 1 that inhibits the binding of free light chain of immunoglobulin to mast cells *in vitro* and inhibition of bronchial constriction in vivo. Given the lack of any additional peptide that can inhibit the binding of free light chain of immunoglobulin to mast cells for treating any disease such as chronic inflammatory bowel disease, viral infection, and multiple sclerosis, one of skill in the art would reasonably conclude

that the disclosure fails to provide a representative number of species of peptides to describe the genus. Thus, Applicant was not in possession of the claimed genus. It also follows that the pharmaceutical composition for treating any disease such as inflammatory bowel disease, viral infection, and multiple sclerosis is not adequately described. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

6. Claims 1-5, 10-13, 16-25 and 31-32 are rejected under 35 U.S.C. 102(b) as being anticipated by Huang *et al* (J Clin Invest 99(4): 732-36, 1997; PTO 1449).

Huang *et al* teaches various compound such as a synthetic peptide AHWSGHCCL produced by a process comprising screening a series of compound such as peptides for it's capability to bind to an immunoglobulin light chain (LC) (See Methods, Table 1, page 734, in particular). The reference peptide is identical to the claimed compound. The reference compound is also identical to the claimed peptide of SEQ ID NO: 1, which has the amino acid sequence AHWSGHCCL for binding with the free light chain of immunoglobulin. The reference compound can reduce the binding of the claimed peptide AHWSGHCCL with immunoglobulin light chain (LC) by 50 %, which is at least 5%, at least 10% at least 25% when the reference compound and reference peptide are present in equimolar amounts (See Table 1 mic, IC_{50} mM, in particular). The reference compound AHWSGHCCL is an LC-binding peptide fragment of Tamm-Horsfall glycoprotein, which is also a derivative of Tamm-Horsfall glycoprotein. The reference compound inherently has a mass less than 10 kDal or less than 2 kDa since the sum of the molecular weight of each of the amino acids (87+155+204+105+75+155+121+121+131) is about 1.15 kDal. Since the reference compound is the same as the claimed compound, it inherently inhibits the binding of free light chain of immunoglobulin (LC) to mast cells when the reference compound is in the presence of an equimolar quantity of the free light chain of immunoglobulin in a solution by at least 5%, and the reference compound competes with the claimed peptide having the amino acid sequence AHWSGHCCL of SEQ ID NO: 1 to reduced the binding of the claimed peptide to the free light chain by at least 75% and at least 90%. Claims 10 and 12 are included in this rejection because the inherently properties of the reference compound is capable of treating a disease such as the ones recited in claim 12 characterized by exhibiting a serum concentration of free light chain of immunoglobulin in serum at least 8 mg/ml or a spinal fluid concentration of free light chain of at least 70 μg/l and/or a spinal fluid concentration of free lambda chain of immunoglobulin of at least 300 μg/l and reduces LC's binding to mast cells

when the reference compound is in the presence of an equimolar quantity of free light chain of immunoglobulin. Claims 13 and 31 are included in this rejection because the reference teaches a pharmaceutical composition comprising the reference compound and a solution such as PBS, which is a pharmaceutical acceptable carrier or diluent (See page 733, column 1, second paragraph, in particular). Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed 1/2/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) Huang et al does not disclose sterile conditions for the production of peptides as required to produce a pharmaceutical composition, and peptides produced of Huang et al are dissolved in PBS for use in vitro test. Thus Huang et al does not disclose a pharmaceutical composition since the peptides disclosed in Huang et al are not sterile and are not prepared for pharmaceutical purpose. (2) Huang does not disclose the use of a LC binding peptide for medical treatment.

In response to applicant's argument that the reference fails to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., sterile condition) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Further, peptides produced of Huang et al are dissolved in PBS, which is a pharmaceutical acceptable carrier.

In response to applicant's argument that Huang does not disclose the use of a LC binding peptide for medical treatment, a product is a product, irrespective of its intended use.

7. No claim is allowed.

8. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be

calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

10. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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March 24, 2003

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3/24/03